REMARKS

Claims 8-12, 15, and 16 have been amended. Claims 1-7, 13, 14, and 17-22 have been cancelled without prejudice or disclaimer. Claims 8-12, 15, and 16 are pending in the instant application. No new matter has been added as a result of the above-described amendments. The objections and rejections set forth in the Office Action have been overcome by amendment.

1. Election/Restriction

The Office Action states that restriction to one of two inventions is required under 35 U.S.C. § 121: (1) the invention of Group I, encompassing claims 1-7 and 17-22, which the Action states are drawn to reagents for detecting HPV and kits comprising the same; and (2) the invention of Group II, encompassing claims 8-16, which the Action states are drawn to methods of detecting HPV. The Action notes that in a telephone interview with Applicants' representative on March 23, 2006, the claims of Group II were provisionally elected with traverse. The Action states that Applicants are required to affirm their provisional election in replying to this Action.

Applicants elect to prosecute claims 8-16, which are designated as Group I, and which the Action states are drawn to methods of detecting HPV. Non-elected claims 1-7 and 17-22 have been cancelled without prejudice or disclaimer.

2. Objections to the claims

The Office Action asserts an objection to claims 8-16 as depending from non-elected claim 1.

Applicant notes that only claim 8 depends from claim 1, and further, that claim 8 has amended claim 8 so that it is no longer depends from non-elected claim 1. Because none of the pending claims depends from non-elected claim 1, Applicants respectfully request that this objection be withdrawn.

The Action also asserts an objection to claim 14 as containing a typographical error.

Applicants have cancelled claim 14 without prejudice or disclaimer, rendering this objection moot.

3. Rejections of claims 8-16 under 35 U.S.C. § 112, second paragraph

The Office Action asserts a rejection of claims 8-16 under 35 U.S.C. § 112, second

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paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter that Applicants regard as the invention.

The Action first asserts that claims 8-16 are indefinite since claim 1, from which claims 8-16 depend, recites the phrase "capable of specifically hybridizing," and it is not clear whether the recited probes have the potential to specifically hybridize or do in fact hybridize to high-risk HPV DNA. The Action suggests that this rejection would be obviated by amending the claims to read "which hybridize."

Applicants, in order to more particularly point out and distinctly claim the subject matter that they regard as their invention, have amended claim 8 (from which the remaining pending claims depend) to recite a method using a reagent that comprises a plurality of genomic HPV DNA probe sets, wherein each genomic HPV DNA probe set comprises a plurality of nucleic acid fragments having different nucleotide sequences that "detectably hybridize" to a plurality of different nucleotide sequences of essentially the full-length genomic sequence of each of the HPV types recited in claim 8. Applicants contend that the pending claims are not indefinite since it is clear that the genomic HPV DNA probe sets recited in the claims specifically hybridize to DNA from high-risk HPV types. Applicants, therefore, respectfully request that this ground of rejection be withdrawn.

The Action next asserts that claims 8-16 are indefinite since claim 1, from which claims 8-16 depend, recites "high-risk HPV DNA" and "low-risk HPV DNA," and neither the claims nor the art set forth a standard for determining whether an HPV type is a high-risk type or a low-risk type. The Action notes, for example, that while the instant application describes HPV types 31, 33, and 51 as being high-risk types, these types are also known in the literature as medium-risk (*i.e.*, intermediate-risk) HPV types.

Applicants respectfully disagree with the Action's assertion that the instant application describes HPV types 31, 33, and 51 as being high-risk types. Applicants note that the instant application explicitly describes HPV types 31, 33, and 51 as being intermediate-risk types (page 1, paragraph 3). Moreover, Applicants contend that at the time U.S. Provisional Application No. 60/105,657 (the '657 application) was filed (*i.e.*, October 26, 1998; the instant application claims the benefit of priority of U.S. Application No. 09/582,492, which claims the benefit of priority of International Application No. PCT/US99/25109, which, in turn, claims the benefit of priority of U.S.

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Provisional Application No. 60/105,657), it was not uncommon for those of ordinary skill in the art to describe HPV types as being either high-risk or low-risk (essentially merging the intermediate-risk and high-risk groups), rather than as being high-risk, intermediate-risk, or low-risk (*see, e.g.*, Togawa *et al.*, 1995, *J. Med. Virol.* 45:435-38; Southern *et al.*, 1997, *Cancer Res.* 57:4210-13; Jacobs *et al.*, 1997, *J. Clin. Microbiol.* 35:791-95; and Gravitt *et al.*, 1998, *J. Clin. Microbiol.* 36:3020-27). In addition, Applicants note that at the time the '657 application was filed, it was not uncommon for those of ordinary skill in the art to describe the HPV types 31, 33, and 51 as high-risk types (*see, e.g.*, Southern *et al.*, 1997; Jacobs *et al.*, 1997; and Gravitt *et al.*, 1998). Applicants also note that at the time the '657 application was filed, the HPV types described in the instant application as being low-risk types (*i.e.*, 6, 11, 42, 43, and 44) were unequivocally understood by those of ordinary skill in the art to be low-risk types, and further, that types 40, 53, 54, and 57 were also understood by those of ordinary skill in the art to be low-risk types (*see, e.g.*, Southern *et al.*, 1997; Jacobs *et al.*, 1997; and Gravitt *et al.*, 1998).

Notwithstanding the fact that some skilled artisans employ an HPV classification scheme that separates HPV types into high-risk and low-risk categories, while other skilled artisans employ a classification scheme that separates HPV types into high-risk, intermediate-risk, and low-risk categories, Applicants contend that such classification schemes are merely shorthand ways of distinguishing HPV types which are known to be associated with malignancy (*i.e.*, carcinogenic HPV types) from HPV types which are known not to be associated with malignancy (*i.e.*, non-carcinogenic HPV types). Applicants contend that while those of ordinary skill in the art, depending on the particular classification scheme that they employ, might disagree as to whether a particular HPV type (*e.g.*, HPV types 31, 33, or 51) is high-risk or intermediate-risk, those of ordinary skill in the art would be able to recognize, or readily determine, whether a particular HPV type is carcinogenic or non-carcinogenic. Applicants contend that because one of ordinary skill in the art, in view of the teachings in the instant specification and knowledge in the prior art, would have been able to readily discern whether a particular HPV type is a low-risk – or non-carcinogenic – type, the pending claims are not indefinite. Applicants, therefore, respectfully request that this ground of rejection be withdrawn.

The Action next asserts that claim 15 is indefinite since it recites that the probes are present in recited amounts, but recites a series of percentages for each probe, and further, because the claim

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does not set forth of what (*e.g.*, hybridization mix, probe mix) the percentages are portions.

Applicants have amended claim 15 to recite a method in which the plurality of nucleic acid fragments of the recited genomic HPV DNA probe sets constitute a certain percentage of the total HPV DNA in the reagent. Applicants contend that because amended claim 15 no longer recites the term "amounts" in combination with a series of percentages, and recites that the percentages are portions of the total HPV DNA in the reagent, amended claim 15 is not indefinite. Applicants, therefore, respectfully request that this ground of rejection be withdrawn.

Applicants respectfully contend that rejections based on 35 U.S.C. § 112, second paragraph, have been overcome by amendment, and request that the Examiner withdraw all rejections made on this basis.

4. Rejections of claims 8-16 under 35 U.S.C. § 112, first paragraph

The Office Action asserts a rejection of claims 8-16 under 35 U.S.C. § 112, first paragraph, as containing subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. The Action states that because the claims do not set forth particular sequences for the probes of the claimed reagent and recite the probes only in terms of their function, the genus of reagents encompassed by the claims includes reagents comprising any probe that is specific to any HPV type that is known to cause cancer, and therefore, that the genus of reagents encompassed by the claims includes hundreds of thousands of possible reagents. Specifically, the Action states that the claims encompass reagents comprising any set of oligonucleotide probes that is specific to any HPV type that is known to cause cancer. The Action also states that because the specification defines "full length" as permitting some sequence variation and shortening of the probes in the claimed reagents, even claims that recite reagents comprising a set of full-length probes encompass reagents comprising a set of oligonucleotide probes. The Action further states that because Applicants describe only a single reagent meeting the functional limitations of the claims, Applicants have express possession of only one species in a genus that comprises hundreds of millions of different possibilities.

As described above in section 3, claim 8 (from which the remaining pending claims depend) was amended to recite a method using a reagent that comprises a plurality of genomic HPV DNA

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probe sets, wherein each genomic HPV DNA probe set comprises a plurality of nucleic acid fragments having different nucleotide sequences that detectably hybridize to a plurality of different nucleotide sequences of essentially the full-length genomic sequence of each of the HPV types recited in claim 8. Applicants note that the instant specification describes the HPV probes of the invention as "*essentially full length genomic* HPV probes" having "*essentially* the same sequence as given in GenBank Accession Numbers: K02718 - type 16; X05015 - type 18; J04353 - type 31; M62877 - type 51; M12732 and A12360 - type 33; M74117 - type 35," and that "[w]hile some sequence variations and shortening of the probe length are permitted, *these are still considered full length and are not similar to oligonucleotide probes as used in the prior art*" (page 5; *emphasis added*). Applicants also note that the sequences described in GenBank Accession Nos. K02718, X05015, J04353, M62877, M12732, A12360, and M74117 range from 7808 to 7912 nucleotides in length, and that HPV-specific oligonucleotides described in the prior art usually range from 30 to 50 nucleotides in length (*see, e.g.*, International Publication No. WO 95/22626,which describes HPV-specific oligonucleotides of 23, 25, 28, and 30 nucleotides in length).

Applicants contend that because amended claim 8 recites a method using a reagent comprising a plurality of *genomic* HPV DNA probe sets, the recited reagent, contrary to the Action's assertion, does not comprise *any* probe that is specific to any HPV type that is known to cause cancer. Applicants also contend that one of ordinary skill in the art, in view of the teachings of the instant application and knowledge in the prior art, would readily understand, for example, that an HPV 16-specific 28-mer oligonucleotide does *not* comprise an *essentially full length* genomic HPV probe having *essentially* the same sequence as that recited in GenBank Accession No. K02718.

In addition, Applicants note that the instant specification teaches that the claimed invention relates to methods of using reagents comprising a plurality of genomic HPV DNA probe sets in which the cross-reactivity of the genomic HPV DNA probe sets is exploited to permit detection of HPV types that are associated with malignancy but which lack genomic sequences that are completely complementary to the genomic HPV DNA probe sets (page 4). Applicants further note that the instant specification teaches the ability of individual genomic HPV DNA probe sets derived from HPV types 16, 18, 31, 33, 35, or 51 to cross-react with the genomic sequences of HPV types 16, 18, 31, 33, 35, 39, 41-45, 51, 52, 56, 58, 59, 68, and 70 (page 17, Table 1). Applicants contend, therefore, that the instant specification clearly contemplates methods of using reagents comprising

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various combinations of genomic HPV DNA probe sets, including a method of using a reagent comprising genomic HPV DNA probe sets derived from HPV types 16, 18, 31, 33, 35, and 51. Applicants, therefore, respectfully disagree with the Action's assertion that the pending claims fail to comply with the written description requirement.

Nevertheless, in an effort to expedite prosecution of the pending claims to allowance, Applicants have amended claim 8 to recite a method for detecting HPV DNA in a cell sample comprising (a) adding a reagent comprising a plurality of genomic HPV DNA probe sets to the cell sample under suitable hybridization conditions, wherein the genomic HPV DNA probe sets comprise a plurality of nucleic acid fragments having different nucleotide sequences that detectably hybridize to a plurality of different nucleotide sequences of essentially the full-length genomic sequences of HPV types 16, 18, 31, 33, 35, and 51; wherein the nucleic acid fragments of the genomic HPV DNA probe sets detectably hybridize to the genomic sequence of HPV types 39, 45, 52, 56, 58, 59, 68 and 70; and wherein the nucleic acid fragments of the genomic HPV DNA probe sets do not detectably hybridize to the genomic sequence of a low-risk HPV type; and (b) determining whether the nucleic acid fragments of the genomic HPV DNA probe sets detectably hybridize to HPV DNA in the cell sample. Applicants contend that because amended claim 8 requires that the use of a reagent comprising genomic HPV DNA probes sets derived from each of HPV types 16, 18, 31, 33, 35, and 51, amended claim 8 complies with the written description requirement.

In view of the teachings in the instant application, Applicants respectfully contend that one of ordinary skill in the art would understand the scope of species comprising the claimed genus of methods, and that the inventors were in possession of the invention having said scope at the time the application was filed. Thus, Applicants respectfully contend that their specification fulfills the requirements of 35 U.S.C. § 112, first paragraph, and request that this ground of rejection be withdrawn.

5. Rejection of claims 8-14 under 35 U.S.C. § 102

a. Rejection of claims 8-14 as being anticipated by Nuovo

The Office Action asserts a rejection of claims 8-14 under 35 U.S.C. § 102(a), as being anticipated by Nuovo, 1998, *Diagnostic Molecular Pathology* 7:158-63. The Action states that

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Nuovo discloses a method which comprises a step of adding a reagent comprising a consensus probe cocktail containing "multiple high HPV types" that detectably hybridizes to HPV types 16, 18, 31, 33, 35, and 51, as well as to HPV types 39, 45, 52, 56, 58, 59, 68, and 70, but not to any of the low risk types tested, and detecting the presence of absence of hybridization inside cells in the sample. The Action also states that the method disclosed by Nuovo anticipates claims 11 and 12, since Nuovo discloses treatment with proteases pepsin and proteinase K, which is a means of deparafinning a cell sample.

To support a rejection under 35 U.S.C. § 102, "the four corners of a single, prior art document [must] describe every element of the claimed invention, either expressly or inherently, such that a person of ordinary skill in the art could practice the invention without undue experimentation." *In re Paulsen*, 30 F.3d 1475, 1479 (Fed. Cir. 1994). The exclusion of even a single claimed element from a reference, no matter how insubstantial or obvious, is enough to negate anticipation. *Connell v. Sears, Roebuck & Co.*, 220 U.S.P.Q. (BNA) 193, 198 (Fed. Cir. 1983). The identical invention must also be shown in the single prior art reference in as complete detail as contained in the application against which the reference is cited. *Richardson v. Suzuki Motor Co.*, 868 F.2d 1226, 1236 (Fed. Cir. 1989). Moreover, the disclosure in an assertedly anticipating reference must provide an enabling disclosure of the desired subject matter; mere naming or description of the subject matter is insufficient, if it cannot be produced without undue experimentation. M.P.E.P § 2121.01; *Elan Pharm., Inc. v. Mayo Found. for Med. Educ. & Research*, 346 F.3d 1051, 1054 (Fed. Cir. 2003); *Amgen, Inc. v. Hoechst Marion Roussel, Inc.*, 126 F. Supp. 2d 69, 88 (D. Mass 2001) (citing *Akzo N.V. v. United States Int'l Trade Comm'n*, 808 F.2d 1471, 1479 (Fed. Cir. 1986)). A reference contains an "enabling disclosure" if the public was in possession of the claimed invention before the date of invention. M.P.E.P § 2121.01. "Such possession is effected if one of ordinary skill in the art could have combined the publication's description of the invention with his [or her] own knowledge to make the claimed invention." *In re Donohue*, 766 F.2d 531 (Fed. Cir. 1985).

Applicants have amended claim 8 (from which the remaining pending claims depend) to recite a method using a reagent comprising a plurality of genomic HPV DNA probe sets that comprise a plurality of nucleic acid fragments having different nucleotide sequences that detectably hybridize to a plurality of different nucleotide sequences of essentially the full-length genomic

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sequences of HPV types 16, 18, 31, 33, 35, and 51, wherein the nucleic acid fragments of the genomic HPV DNA probe sets detectably hybridize to the genomic sequence of HPV types 39, 45, 52, 56, 58, 59, 68 and 70, and wherein the nucleic acid fragments of the genomic HPV DNA probe sets do not detectably hybridize to the genomic sequence of a low-risk HPV type. Applicants contend that the accompanying Declaration Pursuant to 37 C.F.R. § 1.132 of Gerard J. Nuovo (originally submitted in response to the Office Action mailed May 18, 2006 for U.S. Application No. 09/582,492, and submitted herewith as Exhibit A) sets forth affirmative evidence establishing that the Nuovo reference neither describes every element of the reagent recited in claim 8 (*i.e.*, the reagent of claim 1 of U.S. Application No. 09/582,492) such that a person of ordinary skill in the art could practice the claimed invention without undue experimentation nor provides an enabling disclosure of the claimed invention.

In particular, while the Nuovo reference discloses the use of Oncor's high-risk HPV consensus probe to detect the oncogenic HPV types 16, 18, 30, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, and 70, but not the low-risk HPV types 6, 11, 42, 43, and 44, in cervical biopsies by *in situ* hybridization under low stringency conditions (Declaration, para. 3), this reference does not disclose the specific composition of the Oncor high-risk HPV consensus probe – *i.e.*, the particular HPV types comprising the consensus probe or proportions of these particular HPV types (*id.* at para. 4). Thus, using the Nuovo reference's teachings and knowledge in the art at the time that reference was published, a person of ordinary skill in the art would not be able to determine the particular HPV types or proportions of the particular HPV types comprising the Oncor high-risk HPV consensus probe without undue experimentation. More significantly, because a high-risk HPV consensus probe comprising a standard amount of HPV type 16 DNA would detectably hybridize to HPV types 6/11 under conditions of low stringency (*id.* at para. 5), a person of ordinary skill in the art would not be able to prepare a high-risk HPV consensus probe that does not detectably hybridize to the genomic sequence of a low-risk HPV type under low stringency conditions (*id.* at para. 6). Moreover, because the claimed reagent must also detectably hybridize to the genomic sequence of HPV types 39, 45, 52, 56, 58, 59, 68 and 70 (*i.e.*, cross-hybridize with other high-risk HPV types), the inability of the Oncor high-risk HPV consensus probe to detectably hybridize to the genomic sequence of a low-risk HPV type under high stringency conditions is not relevant to the analysis.

Applicants contend that because the Nuovo reference does not describe a reagent that could

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be used to practice the claimed invention, the Nuovo reference does not describe every element of the claimed invention such that a person of ordinary skill in the art could practice the claimed invention without undue experimentation nor provide an enabling disclosure of the claimed invention, the Nuovo reference cannot anticipate the pending claims. Withdrawal of this rejection is therefore respectfully solicited.

b. Rejection of claims 8 and 10-13 as being anticipated by Nuovo *et al.*

The Office Action asserts a rejection of claims 8 and 10-13 under 35 U.S.C. § 102(b), as being anticipated by Nuovo *et al.*, 1995, *J. Histotechnology* 18:105-10. The Action states that Nuovo *et al.* disclose methods that include *in situ* hybridization of HPV genomic probe cocktails to cervical cell samples, and in particular, that Nuovo *et al.* disclose the use of a mixture of probes for HPV types 16 and 18 and a separate mixture of probes for HPV types 31, 33, and 35. The Action also states that each of these probe reagents comprises a "plurality" of DNA probes, since each comprises multiple DNA probe molecules. The Action further states that Nuovo *et al.* disclose a reagent provided by Digene that is derived from the entire genome of the HPV types listed above. With respect to claim 10, the Action states that Nuovo *et al.* disclose the use of low stringency hybridizations conditions, and further, that a probe set comprising full-length genomic probes to HPV types 16 and 18 would be expected to exhibit some hybridization to each of the HPV types recited in claim 10, as evidenced by the instant specification, which demonstrates that these probes are capable of cross-hybridizing to the HPV types recited in claim 10. With respect to claims 11-13, the Action states that Nuovo *et al.* disclose pretreating with the protease trypsin, disclose deparafinning the cell sample, and disclose reagents containing full-length HPV probes.

Applicants note that Nuovo *et al.* disclose a reagent that is derived from the entire genome of HPV types 6, 11, 16, 18, 31, 33, and 35 (as well as three other reagents that are derived from HPV types 6 and 11, HPV types 16 and 18, or HPV types 31, 33, and 35) (page 106). Applicants contend that because Nuovo *et al.* disclose a reagent comprising, at least in part, genomic HPV DNA probe sets derived from HPV types 6 and 11, Nuovo *et al.* does not disclose a method using a reagent in which the nucleic acid fragments of the genomic HPV DNA probe sets do not detectably hybridize to the genomic sequence of a low-risk HPV type, and therefore, that Nuovo *et al.* does not anticipate claims 8 and 10-13. Moreover, Applicants contend that because Nuovo *et al.* also does not disclose

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a method using a reagent comprising genomic HPV DNA probe sets derived from each of HPV types 16, 18, 31, 33, 35, and 51, Nuovo *et al.* does not anticipate the pending claims.

6. Rejections of claims 9 and 14-16 under 35 U.S.C. § 103

a. Rejection of claims 9 and 14 as being unpatentable over Nuovo *et al.* in view of Cox *et al.*

The Office Action asserts a rejection of claims 9 and 14 under 35 U.S.C. § 103(a), as being unpatentable over Nuovo *et al.*, 1995, *J. Histotechnology* 18:105-110 in view of Cox *et al.*, 1995, *Am. J. Obstet. Gynecol.* 172:946-54. With respect to Nuovo *et al.*, the Action states that this reference discloses methods that include *in situ* hybridization of HPV genomic probe cocktails to cervical cell samples, and in particular, that Nuovo *et al.* disclose the use of a mixture of probes for HPV types 16 and 18 and a separate mixture of probes for HPV types 31, 33, and 35. The Action also states that each of these probe reagents comprises a "plurality" of DNA probes, since each comprises multiple DNA probe molecules. The Action further states that Nuovo *et al.* disclose a reagent provided by Digene that is derived from the entire genome of the HPV types listed above. The Action acknowledges, however, that Nuovo *et al.* neither discloses a method using a reagent that hybridizes to the high-risk types listed in claim 9, but not the low-risk types listed in claim 9. With respect to Cox *et al.*, the Action states that this reference discloses methods for detecting HPV in clinical samples using a reagent that hybridizes to all of the HPV types recited in claims 9 or 14. The Action states that it would have been *prima facie* obvious to one of ordinary skill in the art to modify the probe set disclosed by Nuovo *et al.* such that it was similar to the probe set exemplified by Cox *et al.*, so as to provide a comprehensive high-risk cocktail for use in the methods disclosed by Nuovo *et al.*

Applicants note that an analysis of obviousness must be based on the following factual inquiries: (1) the scope and content of the prior art; (2) the differences between the prior art and the claims at issue; (3) the level of ordinary skill in the art at the time the invention was made; and (4) objective evidence of nonobviousness, if any. *Graham v. John Deere Co.*, 383 U.S. 1, 17-18 (1966). Moreover, where claimed subject matter has been rejected as obvious in view of a combination of prior art references, a proper analysis under § 103 *also requires* consideration of two factors: (1) whether the prior art would have suggested to those of ordinary skill in the art that they should make

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the claimed composition or device, or carry out the claimed process; and (2) whether the prior art would also have revealed that in so making or carrying out, those of ordinary skill would have a reasonable expectation of success. *In re Vaeck*, 947 F.2d 488, 493 (Fed. Cir. 1991). As the Federal Circuit has emphasized: "[b]oth the suggestion and the reasonable expectation of success must be founded in the prior art, not the Applicants' disclosure." *Id.*

Applicants note that claim 14 has been cancelled without prejudice or disclaimer. With respect to claim 9, Applicants contend that the accompanying Declaration Pursuant to 37 C.F.R. § 1.132 of Gerard J. Nuovo sets forth affirmative evidence establishing that Nuovo *et al.* in view of Cox *et al.* does not result in a *prima facie* case of obviousness. In particular, while Nuovo *et al.* disclose the use of four high-risk HPV consensus probes obtained from Digene Diagnostics and ONCOR that contain probes generated from specific subgenomic areas of (i) HPV types 16 and 18 or (ii) HPV types 31, 33, and 35 (Declaration, para. 8), this reference does not disclose the specific proportions of the probes in the Digene Diagnostics or ONCOR high-risk HPV consensus probes (*id.* at para. 9). Moreover, because the Cox *et al.* reference does not disclose – and, in fact, persons of ordinary skill in the art other than the inventors did not appreciate at the time the instant application was filed – that a high-risk HPV consensus probe that does not detectably hybridize to the genomic sequence of a low-risk HPV type under low stringency conditions could be prepared by decreasing the proportions of certain probes in the high-risk HPV consensus probe (*id.*, para. 11), the deficiencies and limited disclosure of Nuovo *et al.* cannot be cured by combining the teachings of this reference with those of the Cox *et al.* reference. Applicants contend, therefore, that a person of ordinary skill in the art, using the teachings of Nuovo *et al.* and Cox *et al.* as well as the knowledge in the art at the time these references were published, would not be able to determine the proportions of the HPV probes comprising a high-risk HPV consensus probe that does not detectably hybridize to the genomic sequence of a low-risk HPV type under low stringency conditions (*id.* at para. 10).

In addition, Applicants maintain that one of ordinary skill in the art would not think to substitute the RNA probes of the hybrid capture method disclosed by Cox *et al.* with genomic DNA probes because genomic probes would simply not work in the hybrid capture method disclosed by Cox *et al.* In the hybrid capture method disclosed by Cox *et al.*, single-stranded DNA isolated from a cell sample is allowed to hybridize to RNA probes corresponding to a number of high-risk HPV types, and RNA/DNA hybrids that form are immobilized in a capture tube coated with antibodies

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specific for RNA/DNA hybrids (p. 948). Since the use of a reagent comprising RNA probes is a necessary requirement of the method disclosed by Cox *et al.*, one of ordinary skill would not substitute the RNA probes of this method with genomic DNA probes.

Moreover, because of the substantial differences between the hybrid capture method disclosed by Cox *et al.* and the assay disclosed in the instant application, one of ordinary skill in the art would not have looked to Cox *et al.* for teachings that might be relevant to the assay disclosed in the instant application. For example, at the time the Cox *et al.*, 1995 reference was published, a person of ordinary skill in the art would have appreciated that a hybrid capture probe reagent such as the one disclosed by Cox *et al.* ***would*** detectably hybridize to the genomic sequence of a low-risk HPV type – as well as generate false positives with respect to low-risk HPV types (*id.*, para. 13). In fact, at the time the above-described application was filed, a person of ordinary skill in the art would have expected a high-risk HPV consensus probe to detectably hybridize to the genomic sequence of both low-risk and high-risk HPV types under low stringency conditions, and to not detectably hybridize to the genomic sequence of either low-risk HPV types or high-risk HPV types other than those used to generate the high-risk HPV consensus probe under high stringency conditions (*id.*, para. 14). Clearly, then, Applicants' disclosure in the instant application of a high-risk HPV consensus probe that cross-hybridizes under low stringency conditions with high-risk HPV types other than those used to generate the high-risk HPV consensus probe, while not detectably hybridizing to the genomic sequence of low-risk HPV types, is surprising and unexpected.

Thus, even if one of ordinary skill in the art would not have thought to mix the high-risk HPV consensus probes disclosed by Nuovo *et al.* (*i.e.*, the high-risk HPV consensus probes generated from specific subgenomic areas of HPV types 16/18 and HPV types 31/33/35), absent Applicants' teachings, a skilled artisan would not have been able to determine the proportions of the HPV type-specific probes required to generate a cross-hybridizing high-risk HPV consensus probe that does not detectably hybridize to the genomic sequence of a low-risk HPV type under low stringency conditions. In addition, one of ordinary skill in the art would not have considered preparing DNA – rather than RNA – capture probes, since the former would simply not function in hybrid capture protocol. Finally, one of ordinary skill in the art would not have thought to recreate the RNA probe cocktail of Cox *et al.* using genomic DNA probes because, absent Applicants' teachings, the skilled artisan would not understand that a reagent comprising genomic HPV DNA

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probe sets would allow for the detection of high-risk HPV types ***without*** cross-reacting with low-risk HPV types. Applicants contend that for the reasons listed above, Nuovo *et al.* in view of Cox *et al.* does not result in a *prima facie* case of obviousness with respect to claim 9 or any of the other pending claims. Withdrawal of this rejection is therefore respectfully solicited.

b. Rejection of claims 15 and 16 as being unpatentable over Nuovo *et al.* in view of Cox *et al.*, and further in view of Bauer *et al.*

The Office Action asserts a rejection of claims 15 and 16 under 35 U.S.C. § 103(a), as being unpatentable over Nuovo *et al.*, 1995, *J. Histotechnology* 18:105-110 in view of Cox *et al.*, 1995, *Am. J. Obstet. Gynecol.* 172:946-54, and further in view of U.S. Patent No. 5,639,871 (Bauer *et al.*). The Action's assertions with respect to Nuovo *et al.* and Cox *et al.* are set forth above in section 6(a). While the Action acknowledges that Nuovo *et al.* in view of Cox *et al.* do not disclose the particular concentrations or amounts of each HPV genomic probe set in a reagent, the optimization of hybridization assays by determining ideal probe concentrations was routine in the prior art at the time the invention was made (as exemplified by Bauer *et al.*). The Action asserts that it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have experimented with different probe concentrations so as to arrive at an optimal concentration for the detection of HPV in a sample.

As discussed above, Nuovo *et al.* in view of Cox *et al.* does not result in a *prima facie* case of obviousness with respect to the claimed invention. Because Bauer *et al.* does not disclose – and, in fact, persons of ordinary skill in the art other than the inventors did not appreciate at the time the instant application was filed – that a high-risk HPV consensus probe that does not detectably hybridize to the genomic sequence of a low-risk HPV type under low stringency conditions could be prepared by decreasing the proportions of certain probes in the high-risk HPV consensus probe (Nuovo Declaration, para. 11), the deficiencies and limited disclosure of Nuovo *et al.* in view of Cox *et al.* cannot be cured by combining the teachings of these references with those of Bauer *et al.* In other words, decreasing the proportions of certain probes in the high-risk HPV consensus probe allegedly disclosed by Nuovo *et al.* in view of Cox *et al.* does not constitute optimization. For such experimentation to constitute mere optimization, a form of the high-risk HPV consensus probe allegedly disclosed by Nuovo *et al.* in view of Cox *et al.* that has not been optimized (*i.e.*, one

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containing standard amounts of each HPV type-specific probe) must ***not*** detectably hybridize to the genomic sequence of a low-risk HPV type under low stringency conditions. However, as described in the accompanying Declaration, a high-risk HPV consensus probe comprising a standard amount of HPV type 16 DNA ***would*** detectably hybridize to HPV types 6/11 under low stringency conditions (*id.*, para. 5). Because undue experimentation – and not mere optimization – would be required to prepare the high-risk HPV consensus probe allegedly disclosed by Nuovo *et al.* in view of Cox *et al.*, Applicants contend that Nuovo *et al.* in view of Cox *et al.*, and further in view of Bauer *et al.*, does not result in a *prima facie* case of obviousness with respect to claims 15 and 16 or any of the other pending claims. Withdrawal of this rejection is therefore respectfully solicited.

CONCLUSIONS

Applicants respectfully contend that all conditions of patentability are met in the pending claims as amended. Allowance of the claims is thereby respectfully solicited.

If Examiner Switzer believes it to be helpful, she is invited to contact the undersigned representative by telephone at 312-913-0001.

Respectfully submitted,
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